Perinatal Death

A Clinicopathological Analysis of 99 Cases

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• **The findings at autopsy in 99 cases of perinatal deaths in a ten-year period and on pathologic examination of the accompanying placentas in 39 cases were analyzed clinicopathologically. Also reviewed were the pathologic diagnoses of 225 placentas that were examined for causes other than neonatal death. Cardiovascular and pulmonary problems, particularly hyaline membrane disease, atelectasis and cardiac anomalies were most common. Asphyxia, heart failure and premature placental separation were the most frequent causes of death. In slightly more than half of the cases a reasonable final diagnosis was established by autopsy, and if the placenta was examined, nearly two-thirds could be properly classified. In the remaining 37 per cent, as previously reported in larger series, neither the autopsy nor placental examinations disclosed a satisfactory explanation of the perinatal death.**

INVESTIGATION of perinatal mortality has received considerable support from public health agencies, and large numbers of cases studied at specialized lying-in hospitals have been reported;[4,7,10] but in the community and general hospitals where most people in the United States are now born, it is a relatively neglected field. Statistics on neonatal autopsy examinations are recorded separately in reports to the American Medical Association, suggesting that they are in some way inferior to other autopsies, and the placentas are mostly frozen and processed commercially for chorionic gonadotropin, so that few reach the laboratory for examination.

This would not be important if perinatal mortality rates were declining rapidly, but they are not, as is shown by a tabulation of all deaths of babies weighing over 400 gm. For example:

	Live Births
Chicago Lying-In Hospital (1951-1956)	29.8 per 1,000
Scripps Memorial Hospital (1957)	26.9 per 1,000
Scripps Memorial Hospital (1958)	26.3 per 1,000
Scripps Memorial Hospital (1962)	25.9 per 1,000

The present study was undertaken to analyze the accuracy of the diagnoses made in perinatal deaths and, if possible, to answer the questions:

1. How often is there a failure to make any clinical diagnosis of the cause of death, and how often is the clinical diagnosis correct?

2. How often is the autopsy diagnosis conclusive or inconclusive?

3. How often is a placental examination conclusive, contributory or inconclusive in understanding the cause of death?

4. Should all placentas be examined grossly and microscopically to obtain information regarding problems that may not be clinically evident in the newborn?

For this purpose, the records of perinatal mortality cases with autopsy examinations at a general hospital for a ten-year period (1950-1959) were analyzed by an obstetrician and a pathologist, concerning the clinical history, clinical diagnosis, autopsy and placental pathological findings and the combined usefulness of these items in substantiating or refuting the clinical diagnosis. Records of 99 cases were available, and 39 placentas were examined from this group. In addition all of the 225 placentas that had been examined pathologically during the same period were reviewed.

The routine autopsy procedure included recording body length and weight, the gross weights of heart, lungs, spleen, liver, adrenal glands, kidneys, thymus and brain. Sections were studied from these organs as well as from the pancreas, gonads, accessory sex organs, thyroid, pituitary and bone marrow. Weight and size of the placenta were recorded, and two or three microscopic sections were examined to investigate the marginal sinus, membranes, decidua and chorionic villi.

Five tables were prepared that listed (1) the major autopsy findings, (2) the immediate cause of death assigned by the pathologist, (3) the placental pathologic diagnosis from cases in which autopsy was done, (4) the pathological diagnosis in the cases of all the 225 placentas examined, and (5) the clinicopathological correlations. For comparison the findings in three larger series are also given.[4,6,10]

The clinical diagnosis was correct, as judged by autopsy, in 40 of the 99 cases. The autopsy proved diagnostically conclusive in about 54 per cent of the cases, a lower figure than anticipated. Thirty-nine

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TABLE 1.—*Major Autopsy Findings in Cases of Perinatal Death*

Autopsy Findings	Present Series 99 Cases	Stowens[10] 5,349 Cases No.	Stowens[10] 5,349 Cases Per Cent	Potter[4] 526 Cases No.	Potter[4] 526 Cases Per Cent	Reid[6] 561 Cases No.	Reid[6] 561 Cases Per Cent
Hyaline membrane disease	12	667	12	56	11	134	24
Atelectasis	9	37	1	9	<2	....	....
Cardiovascular anomalies	9	619	12	*	....	....	....
Ventricular septal defects	5	199	....	....	....	....	....
Atrial septal defects	1	134	....	....	....	....	....
Coarctation of aorta	2	47	....	....	....	....	....
Transposition great vessels	1	....	....	....	....	....	....
Intracranial hemorrhage	6	300	6	14	3	....	....
Subarachnoid hemorrhage	3	....	....	....	....	....	....
Cerebral hemorrhage	3	....	....	....	....	....	....
Bronchopneumonia	4	648	12	21	4	75	13
Erythroblastosis fetalis	4	217	4	44	8	....	....
Immaturity	4	807	15	....	....	....	....
Meningitis	4	†196	4	....	....	....	....
Renal Agenesis	2	62	1	*	....	....	....
Hydrocephalus	2	217	4	*	....	....	....
Polycystic kidneys	2	90	2	*	....	....	....
Meningocele	2	153	3	*	....	....	....
Meconium peritonitis	2	27	<1	....	....	....	....
No abnormality or inconclusive	37	2080	39	194	37	....	....

*Total malformations 70 (13%), compared with 17 cases in the present series.
†Includes encephalitis, meningoencephalitis, etc.

placentas examined as a part of autopsy study provided a conclusive or contributory diagnosis in 19 cases (49 per cent). The placental examination was as helpful as the autopsy in establishing the cause of death (Tables 1, 2 and 3).

As shown in Table 1, approximately 38 per cent of the major autopsy findings were of cardiovascular or respiratory conditions that resulted in anoxia. This was comparable with about 41 per cent in Potter's series,[4] 43 per cent of Stowens' material[10] and over 37 per cent in Reid's series.[1,6]

Hyaline membrane disease (respiratory distress syndrome)[3] made up the largest single group, pointing up the urgent need for a means of preventing this frequently fatal condition. Davis[2] found pulmonary disturbances, particularly hyaline membrane disease, the principal causes of death among 256 premature births. All babies with hyaline membrane disease weighed less than six pounds. In ten of twelve cases the birth weight was under five pounds. In most of these pregnancies there were complications which seemed responsible for the premature delivery, although not directly for hyaline membrane disease. In the 75 per cent of infants who weighed less than four pounds an immature chest wall with a flail chest may have existed. This situation would allow the chest wall to retract with each respiratory effort and make it impossible for the alveoli to expand.*

Among fatal cardiovascular anomalies septal defects were the most common. They also made up 199 of 619 cardiac and great vessel anomalies in the cases collected by Stowens,[10] and were the leading cardiac anomaly in his material.

*This mechanism, suggested by Dr. Richard A. Jones of Scripps Memorial Hospital, is being reported elsewhere.

TABLE 2.—*Immediate Cause of Death in 99 Cases of Perinatal Death*

	No. of Cases
Asphyxia	30
(Intrauterine asphyxia 12)	
Heart failure	13
Intracranial hemorrhage	6
Sepsis	5
Atelectasis	4
Erythroblastosis fetalis	3
Pulmonary hemorrhage	2
Undetermined	36

TABLE 3.—*Placental Pathologic Diagnoses from Autopsies*

	Present Series No.	Present Series Per Cent	Potter[4] No.	Potter[4] Per Cent
Premature placental separation	14	36	54	10
Nontoxic separation	10	....	....	....
Ruptured marginal sinus	2	....	11	....
Toxemic separation	2	....	....	....
Massive placental infarction	4	10	....	....
Placenta previa	2	5	5	1
Circumvallate placenta	2	....	....	....
Placentitis	1	....	....	....
Hypoplastic placenta	1	....	....	....
Capillary hemangioma	1	....	....	....
No abnormality	14	....	....	....
Total Cases	39		526	

Erythroblastosis fetalis was diagnosed clinically in four cases. In two cases the autopsy confirmed this diagnosis, but in one case the placenta was not characteristic pathologically. In the fourth case diagnosed clinically, the autopsy was inconclusive and the placental examination was not diagnostic of erythroblastosis. Autopsy demonstrated erythroblastosis in still another case, although this diagnosis had not been made clinically. Thus the clinical, autopsy and

placental findings are all needed sometimes to arrive at the correct diagnosis.

Intracranial hemorrhage was diagnosed correctly clinically in five of six cases in which autopsy was done. In the sixth case intracranial hemorrhage was diagnosed clinically, but hyaline membrane disease was found at autopsy. In the three series of cases reviewed, intracranial hemorrhage, listed by Stowens as due to birth trauma, accounted for from 3 to 6 per cent of the perinatal deaths.[4,6,10]

An immediate cause of death (Table 2) was assigned by the pathologist in 63 of the 99 cases in which autopsy was done. About half of the babies died of asphyxia, one-sixth of heart failure and one-eighth of either cerebral or pulmonary hemorrhage. The remainder died of sepsis, atelectasis and erythroblastosis. Reid[6] believed that hypoxia, malformations and infection are the three major causes of perinatal death. In the present series intracranial hemorrhage and the attendant asphyxia were slightly more common than sepsis.[1,5] Cardiac failure secondary to cardiovascular anomalies was the most common lethal situation that complicated congenital malformations.

The entire series of placentas examined (listed in Table 4) included many that were studied for reasons other than perinatal death. Placentas from cesarean sections, from Rh-negative mothers without evidence of fetal erythroblastosis, from diabetic pregnancies and twin placentas were often submitted.

The two most common placental abnormalities found were premature separation and inflammation secondary to premature rupture of the membranes. In 14 cases it was not possible to confirm by pathological study a clinical diagnosis of placental separation, toxemia of pregnancy or erythroblastosis. Tissue examination of the placenta alone in these conditions cannot be considered either as the exclusive or the definitive diagnostic method, since each of these three abnormalities primarily involves the mother and affects the placenta and fetus secondarily. Only limited amounts of decidua attached to the placenta were usually available for scrutiny.

The most common significant placental abnormality was pathological evidence of a premature separation.[8] Most often this comprised an excessive amount of blood clot attached to and infiltrating a quadrant or more of the maternal surface. Histological examination of this area showed the anchoring decidua to be abnormally vacuolated or hyalinized, and it had evidently lost its elasticity and mechanical stability. The decidual vacuolar degeneration is believed to permit small hemorrhages to form and coalesce, a situation analogous to that which occurs in aortic medionecrosis, predisposing to dissecting hemorrhages of more serious proportions. The basic abnormality is uncertain, but it may be an endocrine

TABLE 4.—*Pathological Examinations of 225 Placentas*

	Number of Cases
Premature separation	23
Marginal sinus rupture	10
Nontoxic separation	10
Toxemic separation	3
Chorionamnionitis	18
Toxemic degeneration	10
Severe infarction	8
Severe hypoplasia	7
Circumvallate placenta	7
Placenta previa	3
Marginal cord insertion with rupture	2
Erythroblastosis fetalis	2
Circummarginate placenta	1
Capillary hemangioma	1
No significant abnormality	143

Clinical Abnormalities Not Confirmed by Placental Examination

Premature separation		6
Toxemic separation	3	
Marginal sinus rupture	2	
Nontoxic separation	1	
Toxemia		5
Erythroblastosis fetalis		3
		14

imbalance, since in a series of women given stilbestrol during pregnancy no nontoxic placental separations occurred, while several were found in the untreated control cases.[9]

When the marginal sinus had ruptured, a blood clot was found localized toward the periphery of the placenta that involved the rounded margin and the adjacent zone of membranous attachment as well as the adjacent cotyledons. Histologically a thrombus was identified within the torn marginal sinus segment with clot spreading by contiguity into the adjacent placenta.

Toxemia of pregnancy complicated by premature placental separation was associated with more serious abnormalities both of the decidua and chorionic villi. The decidua was excessively hyalinized, and the maternal sinusoids thickened. The vessel walls were sclerotic or hyalinized and at times the endothelium was swollen and had a foamy appearance—so-called acute atheroma. In some cases thrombosis of maternal sinusoids was noted. The chorionic villi in toxemia of pregnancy appeared excessively senile for the placental weight and the clinical duration of pregnancy. The trophoblastic cells were abnormally thin and degenerate and had disappeared from parts of the surfaces of many chorionic villi. Excessive intervillous thrombi and infarcts were usually found. The villous stroma was relatively hyalinized and acellular.

The older term *abruptio placentae* has conventionally been used to refer either to nontoxic or toxic placental separations, as well as to ruptured marginal sinus. *Abruptio*, with its inferred meaning of a

TABLE 5.—*Clinicopathologic Correlations*

	No. of Cases
Clinical Diagnoses	
Correct	39
Incorrect	6
Unknown	54
Autopsy Diagnoses	
Conclusive	54
Inconclusive	45
Placental Diagnoses	
Conclusive	14
Contributory	5
Inconclusive	20
No examination	60

dramatic tearing away of the placenta, fails to convey the quiet, unnoticed progressive nature of the process. This obsolete term could be discarded.

Massive infarction was the fourth most common placental diagnosis—in four cases or 10 per cent. While Potter[4] held that there is little evident relation between the degree of placental infarction and neonatal death, in some instances where the placental weight was near the lower limits of normal for the size of the fetus or neonate, and where half or more of the placenta was completely ischemic and degenerated, placental insufficiency due to infarction has been considered acceptable as the cause of death.[2]

In Table 5, which correlates the clinical and pathological diagnoses, the clinical diagnoses were regarded as correct in approximately 40 per cent of the cases. This proportion was not as good as might be anticipated. Also, diagnoses of the cause of death were given as "stillbirth" or "prematurity" in 16 of 31 perinatal fatalities. In the remaining 15 cases a reasonable attempt was made to reach a definite diagnosis. As *stillbirth* and *prematurity* are not acceptable medical diagnoses, the terms should be abandoned in dealing with perinatal mortality.

Autopsy findings were conclusive diagnostically in 54 of the 99 perinatal cases examined. Among the 31 stillbirths, autopsy findings were conclusive in only 14 cases. The autopsy thus was less helpful diagnostically than might have been anticipated, but still was conclusive in over half of the cases. There were 39 placental examinations from the 99 autopsied cases, and in 19 (49 per cent) the pathological findings were conclusive or contributory diagnostically. In the 16 cases where the cause of death was listed clinically merely as stillbirth or prematurity seven of fourteen placental examinations demonstrated a reasonable cause of death, and autopsy established the cause of death in three additional cases.

The clinical diagnosis was found to be either indeterminate or in error in 60 per cent of the present series. If both a pathological examination of the placenta and an autopsy were performed it was possible to assign a reasonably accurate cause of death to nearly two-thirds of the cases that had previously been labeled simply as *stillbirth* or *prematurity*. The placental examination was helpful nearly as often as the autopsy in establishing a final diagnosis. While not all placentas need to be examined pathologically, this would be desirable in all deliveries where fetal distress or the likelihood of a fatality is recognized.

At least two major unsolved problems exist in this field. The most serious is the 37 to 39 per cent of perinatal deaths for which no cause is found by pathological examination. While epidemiological, genetic, statistical and public health investigations[7] provide interesting information concerning the nutritional, racial, geographical, age and other maternal factors that are more or less involved, the problem is in essence individual and medical. More careful histories, physical examinations, laboratory studies and collaborative investigations by interested physicians might be expected to yield answers applicable to mortality of the individual neonate.

The second (probably interrelated) problem is the neglect of the placenta both clinically and pathologically. A prominent obstetrician once said he had seen thousands of placentas and never looked at one. Despite persistent attempts to obtain the placenta in every case of perinatal death, only in 40 per cent of the present series was a pathological examination possible. At least a beginning at investigating the large number of unexplained perinatal deaths could be made if the custom of supplying both the body and placenta to the laboratory became generally established.

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